

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
7 July 2005 (07.07.2005)

PCT

(10) International Publication Number
WO 2005/060748 A1

- (51) International Patent Classification⁷: A01N 43/42, A61K 31/47, C07D 215/18
- (21) International Application Number: PCT/US2004/038593
- (22) International Filing Date: 17 November 2004 (17.11.2004)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data: 60/528,930 11 December 2003 (11.12.2003) US
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- (81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:**
— with international search report
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: FUNGICIDE

(57) Abstract: 5,7-dibromo-8-(2-hydroxyethyl) quinoline and 5,7-dibromo-8-(2-methoxycarbonyloxyethyl) quinoline, fungicidal compositions containing these compounds and methods of treating plant diseases with these compounds.

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Fungicide

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Summary of the Invention

The present invention is directed to the compounds 5,7-dibromo-8-(2-hydroxyethyl) quinoline and 5,7-dibromo-8-(2-methoxycarbonyloxyethyl) quinoline.

15 The present invention is also directed to a method of treating various plant diseases comprising applying to the plant locus a fungicidally effective amount of a fungicide selected from the group consisting of 5,7-dibromo-8-(2-hydroxyethyl) quinoline and 5,7-dibromo-8-(2-methoxycarbonyloxyethyl) quinoline.

The term "plant locus" means the plant itself, its seed, or the soil surrounding said plant.

20 The present invention is further directed to a fungicidal composition comprising 5,7-dibromo-8-(2-hydroxyethyl) quinoline and 5,7-dibromo-8-(2-methoxycarbonyloxyethyl) quinoline and an adjuvant.

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Detailed Description of the Invention

Compositions of the present invention are comprised of a fungicidally effective amount of the compound described above and one or more adjuvants. The active ingredient may be present in such compositions at levels from 0.01 to 05 percent by weight. Other fungicides may also be included to provide a broader spectrum of fungal control. The choice of fungicides will depend on the crop and the diseases known to be a threat to that crop in the location of interest.

The fungicidal compositions of this invention, including concentrates which require dilution prior to application, may contain at least one active ingredient and an adjuvant in liquid or solid form. The compositions are prepared by admixing the active ingredient with an adjuvant including diluents, extenders, carriers, and conditioning agents to provide compositions in the form of a finely-divided particulate solids, granules, pellets, solutions, dispersions or emulsions. Thus, it is believed that the active ingredient could be used with an adjuvant such as a finely-divided solid, a liquid of organic origin, water, a wetting agent, a dispersing agent, an emulsifying agent or any suitable combination of these.

Suitable wetting agents are believed to include alkyl benzene and alkyl naphthalene sulfonates, sulfated fatty alcohols, amines or acid amides, long chain acid esters of sodium isothionate, esters of sodium sulfocuccinate, sulfated or sulfonated fatty acid esters, petroleum sulfonates, sulfonated vegetable oils, ditertiary acetylenic glycols, polyoxyethylene derivatives of the mono-higher fatty acid esters of hexitol anhydrides (e.g., sorbitan). Preferred dispersants are methyl, cellulose, polyvinyl alcohol, sodium lignin sulfonates, polymeric alkyl naphthalene sulfonates, sodium naphthalene sulfonate, and polymethylene bisnaphthalene sulfonate.

- 5 Stabilizers may also be used to produce stable emulsions, such as magnesium aluminum silicate and xanthan gum.

Other formulations include dust concentrates comprising from 0.1 to 60% by weight of the active ingredient on a suitable extender, optionally including other adjuvants to improve handling properties, e.g., graphite. These dusts may be diluted for application at concentrations
10 within the range of from 0.1-10% by weight.

Concentrates may also be aqueous emulsions, prepared by stirring a nonaqueous solution of a water-insoluble active ingredient and an emulsification agent with water until uniform and then homogenizing to give stable emulsion of very finely-divided particles. Or they may be aqueous suspensions, prepared by milling a mixture of a water-insoluble active ingredient and
15 wetting agents to give a suspension, characterized by its extremely small particle size, so that when diluted, coverage is very uniform. Suitable concentrations of these formulations contain from about 0.1-60% preferably 5-50% weight of active ingredient.

Concentrates may be solutions of active ingredient in suitable solvents together with a surface active ingredient. Suitable solvents for the active ingredients of this invention for use in
20 seed treatment include propylene glycol, furfuryl alcohol, other alcohols or glycols, and other solvents which do not substantially interfere with seed germination. If the active ingredient is to be applied to the soil, then solvents such as N,N-dimethylformamide, dimethylsulfoxide, N-methylpyrrolidone, hydrocarbons, and water-immiscible ethers, esters, or ketones.

The concentrate compositions herein generally contain from about 1.0 to 95 parts
25 (preferably 5-60 parts) active ingredient, about 0.25 to 50 parts (preferably 1-25 parts) surface active agent and where required about 4 to 94 parts solvent, all parts being by weight based on the total weight of the concentrate.

5 For application to the soil at the time of planting, a granular formulation may be used. Granules are physically stable particulate compositions comprising at least one active ingredient adhered to or distributed through a basic matrix of an inert, finely-divided particulate extender. In order to aid leaching of the active ingredient from the particulate, a surface active agent such as those listed hereinbefore, or for example, propylene glycol, can be present in the composition.

10 Natural clays, pyrophyllites, illite, and vermiculite are examples of operable classes of particulate mineral extenders. The preferred extenders are the porous, absorptive, preformed particles such as preformed and screed particulate attapulgite or heat expanded, particulate vermiculite and the finely-divided clays such as kaolin clays, hydrated attapulgite or bentonitic clays. These extenders are sprayed or blended with the active ingredient to form the fungicidal

15 granules.

 The granular compositions of this invention may contain from about 0.1 to about 30 parts by weight of active ingredient per 100 parts by weight of clay and 0 to 5 parts by weight of surface active agent per 100 parts by weight of particulate clay.

 The method of the present invention may be carried out by mixing the composition

20 comprising the active ingredient into the seed prior to planting at rates from 0.01 to 50 g per kg of seed, preferably from 0.1 to 5 g per kg, and more preferably from 0.2 to 2 g per kg. If application to the soil is desired, the compounds may be applied at rates from 10 to 1000 g per hectare, preferably from 50 to 500 g per hectare. The higher application rates will be needed for situations of light soils or greater rainfall or both.

25 The compounds of the present invention may be prepared by methods set forth in the following examples:

 Example 1: Preparation of 5,7-dibromo-8-(2-hydroxyethyl)quinoline. A solution of 3.79

5 g of 5,7-dibromo-8-hydroxyquinoline (12.5 mmol) and 975 mL of 2-bromoethanol (13.75 mmol) in 20 mL of dry dimethylformamide containing 5.18 g anhydrous potassium carbonate (37.5 mmol) was placed under argon atmosphere and heated at 60°C with vigorous magnetic stirring. After 4 hr a further 220 µL of 2-bromoethanol was added and stirring continued at 60° overnight. After 22 hr another 440 µL of 2-bromoethanol was added. After 4 days the mixture was poured into 150 mL of water while stirring. The precipitated product was collected by filtration, washed with 50 mL of 0.5 M aqueous potassium carbonate, plain water and air dried. The solid was washed through the funnel by dissolving in dichloromethane, and the solvent was removed to yield 3.18 g of 5,7-dibromo-8-(2-hydroxyethyl)quinoline. After recrystallization from methanol/water containing a little triethylamine, the melting point was 128-131°C.

15 Mass spectrum:

	m/z	intensity
	39.1	3.52%
	43	3.55%
	45.1	5.25%
20	50	3.96%
	51	3.42%
	61	5.65%
	62	10.61%
	63	12.66%
25	64	4.71%
	73	2.06%
	74	9.37%
	75	8.38%
	76	5.58%
30	77	2.82%
	79.9	1.35%
	81.9	1.44%
	85	3.77%
	86	9.38%
35	87	21.29%
	88	21.62%
	89	5.36%
	97.1	1.95%
	98	6.64%

5	99	14.02%
	100	12.06%
	101	5.78%
	102	3.54%
	103	3.99%
10	104	3.30%
	111	1.46%
	112	1.94%
	113	3.10%
	114	50.24%
15	115	52.01%
	116	9.66%
	117	2.76%
	117.9	2.40%
	118.9	3.00%
20	123	1.31%
	124	3.12%
	125	4.26%
	126	23.35%
	127	23.83%
25	128	13.82%
	129	3.19%
	130	2.16%
	135	1.43%
	140	1.92%
30	141	5.05%
	142	2.88%
	143	11.79%
	144	3.03%
	153.9	1.29%
35	156	3.34%
	157.3	1.33%
	165	1.31%
	165.9	1.30%
	166.9	3.03%
40	167.9	1.83%
	169	2.46%
	191.9	1.45%
	193.1	10.45%
	194	38.07%
45	195	14.45%
	196.3	37.26%
	197	5.71%
	203.9	1.61%
	205	8.50%
50	206	24.36%

5	207	13.14%
	208	21.48%
	209	6.66%
	210	1.47%
	220	2.87%
10	221	2.24%
	222	9.39%
	223	5.20%
	224	6.72%
	225	3.29%
15	235	2.33%
	236	1.84%
	237	2.51%
	238	1.65%
	249	1.29%
20	271.9	4.72%
	272.9	10.02%
	273.9	10.25%
	274.9	18.94%
	275.9	6.15%
25	276.9	9.40%
	284.9	3.93%
	285.9	8.03%
	286.9	7.78%
	287.9	12.53%
30	288.9	4.84%
	289.9	5.61%
	298.9	21.19%
	300.9	83.47%
	302	11.84%
35	302.9	99.44%
	303.9	13.05%
	304.9	40.55%
	305.9	4.76%
	311.9	2.48%
40	313.9	54.29%
	315	12.35%
	315.9	100.00%
	316.9	22.81%
	317.9	52.16%
45	318.9	11.09%
	325.9	2.82%
	327	2.55%
	327.9	10.19%
	329	4.30%
50	329.9	11.59%

5	331	2.97%
	331.9	4.63%
	344.9	1.39%
	346.9	2.84%
10	349	1.41%

Example 2: Preparation of 5,7-dibromo-8-(2-methoxycarbonyloxyethyl)quinoline.

Triphosgene, 740 mg (2.5 mmol) was dissolved in 5 mL of anhydrous dioxane and stirred at ambient temperature while 5,7-dibromo-8-(2-hydroxyethyl)quinoline was added in several portions. The mixture was stirred overnight and capped to protect from atmospheric moisture.

15 The solvent and excess reagent were removed under a stream of dry argon. Residue was redissolved in 10 mL of methanol, stirring for 1 hr., and the solvent was removed. The residue was recrystallized from methanol/water. Melting point: 102.5104.5°C.

20 Proton NMR in CDCl_3 : 3.44 (s, 3H, CH_3O -), 3.74 (t, 2H, $J=4.8$, $-\text{OCH}_2\text{CH}_2-$), 4.48 (t, 3H, $J=4.8$, $-\text{OCH}_2\text{CH}_2-$), 7.56 (m, 1H, ArH), 8.03 (s, 1H, ArH between two Br), 8.49 (m, 1H, ArH)

Carbon- 13 NMR in $\text{DMSO}-d_6$:

	ppm	Assignment
	58.12	$-\text{CH}_3\text{O}-$
25	68.47	$-\text{OCH}_2\text{CH}_2-$
	69.32	$-\text{OCH}_2\text{CH}_2-$
	115.95	ArC, 8-position
	119.26	ArC, ring fusion
	124.06	ArC, 3-position
30	127.10	ArC, 5-position
	132.61	ArC, 6-position
	135.55	ArC, 4-position
	141.33	ArC, 7-position
	144.25	ArC, ring fusion
35	151.63	carbonyl
	152.52	ArC, 2-position

Mass spectrum:

	m/z	intensity
40	43.1	2.86%
	44	0.57%
	45.1	5.85%

5	50	0.58%
	51	0.56%
	58.1	1.20%
	59.1	44.11%
	60.1	1.51%
10	61	1.56%
	62	2.29%
	63	3.95%
	64	1.04%
	73	0.67%
15	74	1.84%
	75	1.59%
	76	1.00%
	85	1.08%
	86	3.09%
20	87	8.10%
	88	6.19%
	89	0.99%
	96.5	0.57%
	98	1.44%
25	99	3.73%
	100	2.42%
	101	0.72%
	102	0.78%
	112	0.86%
30	113	1.51%
	114	28.34%
	115	9.58%
	116	1.51%
	117	0.69%
35	117.9	0.58%
	118.9	0.60%
	124	1.00%
	125	1.55%
	126	8.21%
40	127	2.08%
	128	2.17%
	129	1.65%
	130	0.64%
	140	0.69%
45	141	1.12%
	142	1.12%
	143	3.27%
	144	0.67%
	164.9	0.59%
50	166	0.71%

5	166.9	0.93%
	168	0.76%
	192	0.87%
	193	8.20%
	194	8.79%
10	195	8.38%
	196	7.84%
	197	0.96%
	204	0.84%
	205	4.83%
15	206	3.61%
	207	6.91%
	208	3.33%
	209	1.25%
	221	1.08%
20	222	2.49%
	223	1.63%
	224	2.30%
	225	0.62%
	236	0.58%
25	271.9	7.11%
	272.9	3.23%
	273.9	13.71%
	274.9	6.15%
	275.9	7.07%
30	276.9	2.93%
	283.9	2.12%
	285	0.57%
	285.9	4.98%
	286.9	1.21%
35	287.9	3.68%
	288.9	0.93%
	289.9	0.87%
	298.9	1.73%
	300.9	54.81%
40	302.9	100.00%
	303.9	11.49%
	304.9	48.26%
	305.9	5.14%
	306.9	0.34%
45	311.9	0.32%
	313.9	3.11%
	315	1.10%
	315.9	5.38%
	316.9	2.06%
50	317.9	2.79%

5	318.9	0.98%
	325.9	0.19%
	327.9	2.84%
	329.9	5.00%
	331	0.80%
10	331.9	2.38%
	332.9	0.30%
	374	0.12%
	402.9	0.65%
	405	1.31%
15	406	0.28%
	407	0.64%
	407.9	0.13%

The fungicide of Example 1 has been evaluated by the following procedures:

20 Contact evaluation.

Compound solution: Contact evaluations were conducted to determine the anti-fungal activity of each compound against *Botrytis cinerea*, *Sclerotinia sclerotiorum*, *Pythium aphanidermatum*, *Rhizoctonia solani*, *Cercospora arachidicola*, *Mycosphaerella fijiensis*, and *Monilinia laxa*. Five milligrams of each compound were dissolved in 0.5 milliliter of DMSO for
 25 a compound stock solution of 1.0% w/v. Compound stock solutions were serial diluted with DMSO to 20, 10, and 2 ppm final well concentration.

Fungi preparation: *Botrytis cinerea* spores were taken from 6-week-old cultures grown at 22C on full strength potato dextrous agar (PDA) plates. *Sclerotinia sclerotiorum*, *Pythium aphanidermatum*, *Rhizoctonia solani*, and *Monilinia laxa* mycelia were taken from 4- to 10-day-
 30 old shake flask cultures grown at room temperature on full strength potato dextrous broth (PDB). *Cercospora arachidicola* mycelia were taken from 10- to 14-day-old shake flask cultures grown at room temperature on a full strength PDB amended with peanut oil. *Mycosphaerella fijiensis* mycelia were taken from 10- to 14-day-old shake flask cultures grown at room temperature on V8 juice broth. *Sclerotinia sclerotiorum*, *Pythium aphanidermatum*, *Rhizoctonia solani*,

5 *Cercospora arachidicola*, and *Mycosphaerella fijiensis* mycelia (0.4 g mycelia) were blended for 45 seconds in 20 mL sterile de-ionized water. *Monilinia laxa* mycelia (1 g mycelia) was blended for 45 seconds in 30 mL of sterile de-ionized water. *Botrytis cinerea* spores were diluted with quarter strength PDB to 1×10^5 spores/mL final well concentration. All mycelia were diluted in water (1:5 mycelia:water) before distributing into the wells.

10 Microtiter plate preparation: Compound solution (10 :L), quarter strength PDB (900 :L) and fungi preparation (100 :L) were sequentially distributed into 48-well microtiter plates (n= 3 replications/compound/rate). A blank consisted of quarter strength PDB and fungi preparation. Commercial fungicide controls (100 ppm diluted with water) consisted of Scala for *Botrytis cinerea*, Dithane F-45 for *Mycosphaerella fijiensis*, and Benlate for *Sclerotinia sclerotiorum*,
15 *Pythium aphanidermatum*, *Rhizoctonia solani*, *Cercospora arachidicola*, and *Monilinia laxa*. Plates were shaken in a circular rotator at room temperature for 20 minutes, then incubated at 25C for 24 to 72 hours, depending on the pathogen.

Fungal control ratings: Fungal growth in wells containing the compounds were compared to the positive control and fungal inhibition was rated as full, partial, or none. Final readings
20 were the average of the three wells (Table 1).

Detached bean leaf bioassay

Compound solution: Compound solutions were prepared by diluting compound stock solutions (1.0% w/v compound in DMSO) to 200 ppm with 0.01% w/v Triton X-100.

25 Spore solution preparation: *Botrytis cinerea* spores were taken from 6-week-old cultures grown at 22C on full strength potato dextrous agar (PDA) plates and harvested in 1:16 frozen orange juice concentrate:water. *Botrytis cinerea* spore solutions were prepared by diluting spore

5 cultures to 5×10^4 spores/mL with 1:16 frozen orange juice concentrate:water.

Plant material: Middle trifoliate leaves of greenhouse grown *Phaseolus vulgaris* (Bush bean cv. Blue Lake 274) were excised and placed on a plastic grid above a tray containing moist towels.

Treatment method: One half of the adaxial surface of the leaf was treated with the
10 compound solution (100 :L) using a 3 cm Bacti Cell Spreader. A blank consisted of 0.01% w/v Triton X-100. A commercial fungicide control (200 ppm diluted with water) consisted of Scala. After the solutions dried, the trays containing the leaves were covered and held one day in a growth chamber (22C). The adaxial surfaces of the leaves were then inoculated with 5-60 :L droplets of *Botrytis cinerea* spore solution.

15 Fungal control rating: Three days after inoculation with *Botrytis*, the percent necrotic area under the inoculation droplet was determined. Since the areas under the blank (0.01% w/v Triton X-100) were 100% infected, fungal control was expressed as 100 minus the percent necrotic area, and thus 0% infected is 100% fungal control (n = 3 leaves/compound, 5 inoculation droplets/leaf, Table 2).

20 Phytotoxicity ratings: Phytotoxicity was rated as 0 = no phytotoxicity, 1=slight phytotoxicity, 2=moderate phytotoxicity, or 3=excessive phytotoxicity (Table 2).

The fungicide of Example 1 has demonstrated the following activity.

5

Table 1. Fungal control of *Rhizoctinia solani*, *Pythium aphanidermatum*, *Monilinia laxa*, *Botrytis cinerea*, *Cercospora arachidicola*, *Sclerotinia sclerotium*, and *Mycosphaerella fijiensis* by compounds in contact evaluations.

Control of fungi (full, partial, none)		
Organism	Fungicide rate (ppm)	
<i>Rhizoctinia solani</i>	20	Full
	10	Full
	2	Full
<i>Pythium aphanidermatum</i>	20	Full
	10	Full
	2	Full
<i>Monilinia laxa</i>	20	Full
	10	Full
	2	Full
<i>Botrytis cinerea</i>	20	Full
	10	Full
	2	Partial
<i>Cercospora arachidicola</i>	20	Full
	10	Full
	2	None
<i>Sclerotinia sclerotium</i>	20	Full
	10	Full
	2	Full
<i>Mycosphaerella fijiensis</i>	20	Full
	10	Full
	2	Full

5

Table 2. Fungal control of <i>Botrytis cinerea</i> by compounds in a detached bean leaf (<i>Phaseolus vulgaris</i>) bioassay and bean leaf phytotoxicity ratings.	
Botrytis cinerea control (200 ppm)	100%
Phytotoxicity (200 ppm)	Slight

5 In the Claims

1. 5,7-Dibromo-8-(2-hydroxyethyl) quinoline.
2. 5,7-Dibromo-8-(2-methoxycarbonyloxyethyl) quinoline.
3. A fungicidal composition comprising the compound of claim 1 and an adjuvant.
4. A fungicidal composition comprising the compound of claim 2 and an adjuvant.
- 10 5. A method of treating plant diseases comprising applying to the plant locus a fungicidally effective amount of the compound of claim 1.
6. A method of treating plant diseases comprising applying to the plant locus a fungicidally effective amount of the compound of claim 2.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US04/38593

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A01N 43/42 ; A61K 31/47 ; C07D 215/18

US CL : 424/405 ; 514/311 ; 546/180, 152

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/405 ; 514/311 ; 546/180, 152

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN STRUCTURE SEARCH, FILE CAPLUS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4,472,404 (PAXTON et al) 18 September 1984 (18.09.1984), compound 2 in table I in columns 3-4.	1-6

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search

27 January 2005 (27.01.2005)

Date of mailing of the international search report

22 FEB 2005

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